(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/24777 A1

(51) International Patent Classification[7]: A61K 9/16, 9/28, 9/20

(21) International Application Number: PCT/EP00/09576

(22) International Filing Date: 29 September 2000 (29.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9923436.1 4 October 1999 (04.10.1999) GB

(71) Applicant *(for all designated States except US)*: **AMERICAN HOME PRODUCTS CORPORATION** [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **MUIR, Ian, Stuart** [GB/GB]; 22 Chase Farm Close, Waltham Chase, Hampshire SO32 2UD (GB). **POTTS, Angela, Catherine** [GB/GB]; Allind, Brownwich Land, Titchfield, Hampshire PO14 4NY (GB). **ROWLEY, Michael, John** [GB/GB]; 187 Segensworth Road, Titchfield, Hampshire PO15 5EH (GB). **SIMS, Edward, Eric** [GB/GB]; Friar Wood, Martin Street, Bishops Waltham, Hampshire SO32 1DN (GB). **WILSON, Christopher, Steven** [GB/GB]; 17 Alver Road, Gosport, Hampshire PO12 1QP (GB).

(74) Agents: **TALBOTT, Dawn, Jacqueline** et al.; Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/24777 A1

(54) **Title:** NOVEL PHARMACEUTICAL COMPOSITIONS

(57) **Abstract:** Novel pharmaceutical compositions are provided, in particular oral formulations for once a day administration of a drug/medicament and to novel solid dose units for incorporation therein are provided. The solid dose units provide a phased release of drug to target or prolong the pharmaceutical effect. The compositions are particularly useful for multiphase delivery of proton pump inhibitors such as lansoprazole, pantoprazole, omeprazole, perprazole, etc.

NOVEL PHARMACEUTICAL COMPOSITIONS

The present invention relates to novel pharmaceutical compositions such as oral formulations for once a day administration of a drug/medicament and to novel solid dose units for incorporation therein. The solid dose units provide a phased release of drug to target or prolong the pharmaceutical effect. The compositions are particularly useful for multiphase delivery of proton pump inhibitors such as lansoprazole, pantoprazole, omeprazole, perprazole, etc.

The treatment of certain medical conditions requires an effect to be achieved over a 24 hour period, e.g. in conditions such as duodenal ulcers, peptic ulcers and reflux oesophagitis there is a need to control gastric pH. Similarly in the treatment of rheumatoid arthritis there is a need to control pain and ease mobility difficulties and in the treatment of patients with high blood pressure there is a need to control blood pressure. Immediate release dosing regimes often result in periods during the day where the desired effect is not achieved and so such conditions are often treated with multiple doses of drug each day, but this is inconvenient and can lead to reduced patient compliance. These conditions are often treated with sustained release formulations but if there is not a constant requirement for the drug during the 24 hour period this can lead to the use of more drug than necessary. Frequently there is not a constant requirement for the drug, i.e. when an initial dose of the drug is capable of achieving the desired effect and it is only as this effect begins to diminish that further drug is required. Another example is when symptoms may only occur intermittently, perhaps at particular times of the day, e.g. during the night or early in the morning.

In the treatment of conditions such as duodenal ulcers, peptic ulcers and reflux oesophagitis with proton pump inhibitors there are benefits in increasing the time that the intragastric pH is maintained above 3.0, preferably above 4.0, in particular there are benefits in maintaining the pH above 3.0, preferably above 4.0, over a 24 hour period. Current immediate release dosing regimes often result in periods during the day where this is not achieved and this may become particularly acute at night where "breakthrough pH" occurs. There is not a constant requirement for the inhibitor because it is postulated that the initial dose inhibits the receptors and it is only when the receptors begin to regenerate that further inhibitor is required. The use of sustained release formulations therefore involves the use of more inhibitor than necessary. It is desirable to

provide pulsed release formulations capable of releasing a second dose of inhibitor when the effects of the first dose begin to diminish.

There is a need for pharmaceutical formulations capable of delivering drug at timed periods during 24 hours when a condition and/or symptom occurs or reoccurs, in particular formulations capable of providing pulsed release of a drug, where the drug is released in at least two pulses, the second pulse releases drug when the effect of the first release is at least partially diminished and, if applicable, any further pulses also release drug when the effects of the previous pulse are at least partially diminished. There is also a need for pharmaceutical formulations capable of providing a single daily dose of a drug affecting gastric pH such as a proton pump inhibitor, in particular formulations capable of maintaining the gastric pH above about above 3.0, preferably above 4.0, for a period of about 24 hours after a single daily dose, e.g. formulations capable of delivering drug at timed periods during 24 hours when an increase in pH is expected.

In the treatment of conditions where symptoms occur at a known period of the day, e.g. during the night, as the patient wakes or as the patient gets out of bed, it is desirable to treat the symptoms in advance so that they can be avoided or at least minimised. Again sustained release formulations can be used, e.g. before the patient goes to bed, but they often result in the use of more drug than required. There is therefore a need for delayed release formulations capable of releasing drug in anticipation of symptoms. A formulation which could be taken at night and which would release the drug the following morning so that its effects are achieved before the patient wakes would be particularly advantageous. The formulation could suitably include multiple doses such that it can be taken to provide immediate relief followed by further relief after a predetermined period of time. One condition which could be treated with such a formulation is rheumatoid arthritis. Patients suffering from rheumatoid arthritis experience difficulty in moving when they wake and so it would be advantageous to provide a formulation which could be taken at night and which would release the drug the following morning so that its effects are achieved before the patient wakes. The formulation could suitably include multiple doses such that it can be taken during the day to provide immediate relief in addition to relief the following morning.

There is a need for delayed release formulations capable of releasing drug after a predetermined delay, preferably being such that the delayed release of the drug coincides with and/or anticipates the occurrence or reoccurrence of the symptom or condition to be treated.

The present invention addresses one or more of the problems discussed above. It has been found that the inclusion of a disintegrant in the core of a solid dose unit, surrounded by an outer semi-permeable membrane comprising a permeable water insoluble polymer and at least 50 % by weight glidant surprisingly provides the desired delay and subsequent release profile. The novel formulation is capable of delaying the release in a largely pH independent manner. After the period of delay, drug release is immediately initiated.

The delay and the subsequent release profile can be manipulated by the selection of the composition and/or thickness of the semi-permeable membrane and/or the composition and/or amount of disintegrant included in the core. The arrangement of the disintegrant in the core can also be adapted to influence the delay and subsequent release profile, e.g. it can be included as a separate outer layer of the core.

A first aspect of the invention provides a solid dose unit for the delayed release of a drug comprising:

a) a core comprising the drug and at least one disintegrant

and b) an outer semi-permeable membrane surrounding the core which comprises a permeable water insoluble polymer and at least 50 % by weight glidant.

The solid dose units may suitably be pellets, mini-tablets, granules, tablets etc. which are well known in the art. The drug may be included in the units by any suitable conventional means, e.g. it may be incorporated in the core material or it may be applied to a seed core as a coat, with or without other constituents which make up the unit. The drug and the disintegrant may be included as separate layers of the core or they may be mixed together in the core.

The units are preferably such that when they are subjected to in-vitro exposure to simulated intestinal fluid minimal drug is released until after at least four

hours exposure and substantially all of the drug is released after 24 hours exposure. Preferred embodiments are those wherein minimal drug is released until after at least six hours in-vitro exposure to simulated intestinal fluid. Further embodiments of the invention are those which provide minimal drug release until after at least 8, 9, 10, 11 and 12 hours in-vitro exposure to simulated intestinal fluid respectively. For each of these embodiments substantially all of the drug is released after 24 hours in-vitro exposure to simulated intestinal fluid, more preferably substantially all of the drug is released after 22 hours in-vitro exposure to simulated intestinal fluid.

The in-vitro dissolution profile may be determined by techniques known in the art, for example using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results should vary only a little depending on the method of measurement.

Theoretically one should be able to measure 100% release of the drug after in vitro exposure to simulated intestinal fluid. However, in practice this if often not attainable and no more than, e.g. 85 % of the drug can be measured after even a very long period of time. This is due in part to limitations inherent in the detection equipment, but also to the fact that certain drugs may break down to other chemicals and hence go undetected or a small proportion may take a very long time to release. The point at which "substantially all the drug has been released" is therefore taken to be the point at which no further increase in the amount of drug released is seen, i.e. when minimal further release is seen. All other measurements, i.e. percentages are measured against the total drug included in the formulation.

In another embodiment of the invention less than 10% of the drug is released after four hours in-vitro exposure to simulated intestinal fluid, at least 30% is released after ten hours exposure and at least 70% is released after 24 hours exposure, preferably at least 70% is released after 20 hours exposure. These measurements are cumulative, i.e. the term "is released after" indicates the total amount of released drug that is measured at the stated time, i.e. after 4, 10 or 20 hours in-vitro exposure to simulated intestinal fluid.

In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure to simulated intestinal fluid, at least 35% is released after ten hours exposure and at least 75% is released after is released after 24 hours

exposure, preferably at least 75% is released after 20 hours exposure. In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure to simulated intestinal fluid, at least 40% is released after ten hours exposure and at least 80% is released after 20 hours exposure.

In another embodiment of the invention less than 10% of the drug is released after six hours in-vitro exposure, at least 30% is released after ten hours and at least 70% is released after 24 hours, preferably at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 35% is released after ten hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 8 hours in-vitro exposure, at least 30% is released after 12 hours and at least 70% is released after 24 hours, preferably at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 35% is released after 12 hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 10 hours in-vitro exposure, at least 30% is released after 14 hours and at least 70% is released after 24 hours exposure, preferably at least 70% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 35% is released after 14 hours and at least 75% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 40% is released after 14 hours and at least 80% is released after 22 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 12 hours in-vitro exposure, at least 30% is released after 16 hours and at least 70% is released after 24 hours. In a further embodiment less than 5% of the drug is released after 12 hours in-vitro exposure, at least 35% is released after 16 hours and at least 75% is released after 24 hours. In a further embodiment less

than 5% of the drug is released after 12 hours in-vitro exposure, at least 40% is released after 16 hours and at least 80% is released after 24 hours.

Suitable disintegrants include croscarmellose sodium, crospovidone, sodium starch glycolate etc. These materials result in swelling and disintegration of the dosage unit.

The semi-permeable membrane comprises a permeable water insoluble polymer and at least 50 % by weight glidant. The weight of the glidant accounts for at least 50% of the total weight of the membrane. The semi-permeable membrane may optionally comprise further components, but preferred embodiments are those wherein the membrane comprises the permeable water insoluble polymer and the glidant only.

The semi-permeable membrane preferably comprises at least 55% glidant, more preferably at least 60% glidant and most preferably at least 65% glidant. Particular embodiments of the invention include a semi-permeable membrane which comprises at least 66 % glidant.

Suitable glidants include talc, silicon dioxide, kaolin, glycerol monostearate, metal stearates such as magnesium stearate, titanium dioxide and starch. preferred glidants are talc, silicon dioxide and kaolin. The most preferred glidant is talc. Pharmaceutical compositions usually comprise less than 30% glidants such as talc, however the function of the glidant in the present invention is completely different from the conventional function, the high level of glidant included in the semi-permeable membrane affects the mechanical and physical properties of the membrane. Suitable polymers include methacrylic acid polymers such as Eudragits, addition polymers such as PVAP, PVP and PVA, cellulose derivatives such as cellulose acetate, ethylcellulose, cellulose acetate succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose and suitable resins such as shellac. Preferred polymers are methacrylic acid derivatives, ethylcellulose and cellulose acetate. The most preferred polymers are methacrylic acid polymers such as Eudragits, particularly Eudragit RS. The membrane preferably lacks a plasticiser.

The semi-permeable membrane is surprisingly capable of resisting pressure from the swelling of the disintegrant material until a critical point at which it ruptures and drug release immediately commences.

The units preferably release the drug in a non-osmotic, largely pH independent manner. The units preferably lack protection from the environment of the stomach, e.g. they lack an enteric coat. The units preferably lack osmotic modifiers.

The units are particularly suitable for the controlled release of proton pump inhibitors, preferably lansoprazole, pantoprazole, omeprazole, perprazole, etc. They may be included in formulations suitable for the treatment of duodenal ulcers, peptic ulcers and reflux oesophagitis. The units are also suitable for the controlled delivery of other drugs, e.g. drugs that are conventionally administered in multiple doses or when timing is important for the reasons discussed above. Drugs which may be included in the units include, e.g. proton pump inhibitors, anti-inflammatories, antihypertensives, antibiotics, hormonal drugs and drugs which are active on the endocrine system. The term proton pump inhibitor when used herein refers not only to the active compounds but also to appropriate prodrugs and derivatives. The term also covers appropriate salts of the compounds, prodrugs and derivatives.

The cores may suitably comprise one or more of the following: a stabiliser such as magnesium carbonate; a binder such as hydroxypropylcellulose LF grade or EXF grade; a disintegrant such as hydroxypropylcellulose (low substituted) 1-hpc 31; a binder or diluent such as sucrose, maize starch; and/or a lubricant such as magnesium stearate.

A second aspect of the invention provides a plurality of solid dose units as described above which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after four hours exposure less than 10% of the drug is released

ii) after ten hours exposure at least 30% drug is released

and iii) after 24 hours exposure at least 70% drug is released.

After four hours in-vitro exposure to simulated intestinal fluid less than 10% of the drug is released, preferably less than 7% is released, more preferably less than 5% is released and most preferably less than 2% is released. Preferred embodiments are those wherein after six hours in-vitro exposure to simulated

intestinal fluid less than 10% of the drug is released, preferably less than 7% is released, more preferably less than 5% is released and most preferably less than 2% is released. Further embodiments of the invention are those wherein after at least 8, 9, 10, 11 and 12 hours in-vitro exposure to simulated intestinal fluid respectively less than 10% of the drug is released, preferably less than 7% is released, more preferably less than 5% is released and most preferably less than 2% is released. For each of these embodiments after ten hours in-vitro exposure to simulated intestinal fluid at least 50% of the drug is released, preferably at least 55% is released, more preferably at least 60% is released and most preferably at least 65% is released. For each of these embodiments after 24 hours in-vitro exposure to a simulated intestinal fluid at least 70% of the drug is released, preferably at least 75% is released, more preferably at least 80% is released.

In one embodiment of the invention less than 10% of the drug is released after four hours in-vitro exposure, at least 30% is released after ten hours and at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure, at least 35% is released after ten hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In another embodiment of the invention less than 10% of the drug is released after six hours in-vitro exposure, at least 30% is released after ten hours and at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 35% is released after ten hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 8 hours in-vitro exposure, at least 30% is released after 12 hours and at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 35% is released after 12 hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 10 hours in-vitro exposure, at least 30% is released after 14 hours and at least 70% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 35% is released after 14 hours and at least 75% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 40% is released after 14 hours and at least 80% is released after 22 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 12 hours in-vitro exposure, at least 30% is released after 16 hours and at least 70% is released after 24 hours. In a further embodiment less than 5% of the drug is released after 12 hours in-vitro exposure, at least 35% is released after 16 hours and at least 75% is released after 24 hours. In a further embodiment less than 5% of the drug is released after 12 hours in-vitro exposure, at least 40% is released after 16 hours and at least 80% is released after 24 hours.

A third aspect of the invention provides an oral formulation for the controlled release of a drug which comprises solid dose units as described above. These include oral formulations for the controlled release of a drug which comprises a first population of solid dose units comprising the drug and a second population of solid dose units comprising the drug wherein the first population comprises units which exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after two hours exposure at least 60% of the total drug included in the first population is released

and ii) after three hours exposure at least 80% of the total drug included in the first population is released

and the second population comprises units as described above.

The units of the first population are preferably such that after two hours in-vitro exposure to simulated intestinal fluid at least 65% of the total drug included in the first population is released, more preferably at least 70% is released, most preferably at least 75% is released. The units of the first population are preferably such that after three hours in-vitro exposure to simulated intestinal fluid at least 80% of the total proton pump drug included in the first population

is released, more preferably at least 85% is released, most preferably at least 90% is released.

The units of the invention may be included in any suitable oral formulation, e.g. tablets, capsules and microcapsules. Other examples will be apparent to a person of skill in the art, as will suitable excipients and for inclusion in the formulations.

The units of the first population preferably release the drug when the formulation or the units pass from the stomach into the intestine as a result of the change in pH. This may be achieved by known means, e.g. by coating the units with an enteric coat. The change in pH when the environment of the duodenum is reached causes the enteric coat to dissolve and release the drug. Suitable materials from which enteric coats may be prepared are well known in the art, e.g. cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, Preferred materials are Eudragit S100, Eudragit L 100, Eudragit L 100.55 and Eudragit L30D-55, most preferably Eudragit L30D-55.

The formulations are suitable for the multiphase delivery of proton pump inhibitors, preferably lansoprazole, pantoprazole, omeprazole or perprazole. These formulations are suitable for the treatment of duodenal ulcers, peptic ulcers and reflux oesophagitis. The formulations are also suitable for the phased delivery of other drugs, e.g. drugs that are conventionally administered in multiple doses or at as sustained release formulations for the reasons discussed above. Drugs which may be included in the formulations include, e.g. proton pump inhibitors, anti-inflammatories, antihypertensives, antibiotics, hormonal drugs and drugs which are active on the endocrine system. The drug included in the first and second populations of units may be different or identical. Preferred formulations are those in which the drug included in the first and second populations of units are identical. The amount of drug included in the first and second populations of units may be different or identical.

The units may suitably be incorporated in a delivery system which provides multiphased delivery of a drug, i.e. which provides at least two phases of delivery from a single dosage formulation. Further phases of delivery can be provided by including further populations of solid dose units adapted to deliver drug after a different period of delay. The time interval between phases can be manipulated by the selection of the composition of the units, i.e. the selection of

the composition and/or thickness of the semi-permeable membrane and/or the composition and/or amount of disintegrant included in the core and/or the arrangement of the disintegrant in the core of each population.

The formulations are preferably suitable for once daily administration. They are preferably suitable for controlling gastric pH over a 24 hour period. Particularly preferred formulations are those capable of controlling gastric pH over a 24 hour period so as to prevent the pH falling below 4.0 over this period.

The present invention also provides a composition comprising a permeable water insoluble polymer and at least 50 % by weight of glidant which is suitable in the preparation of the solid dose units described above. The composition more preferably comprises at least 55% by weight glidant, even more preferably at least 60% glidant and most preferably at least 65% by weight glidant. Particular embodiments of the invention include at least 66 % by weight glidant. Preferred glidant materials include talc, silicon dioxide, kaolin, glycerol monostearate, magnesium stearate and other metal stearates, the most preferred glidant is talc. The polymer may suitably be a methacrylic acid polymers, e.g. a Eudragit.

The present invention still further provides a method for the preparation of the solid dose units described above which comprises coating a core comprising a drug and a disintegrant with a composition comprising a permeable water insoluble polymer and at least 50 % by weight glidant. The present invention also provides a method for the preparation of the oral formulations described above which comprises bringing solid dose units as described above into association with suitable components to provide a pellet, mini-tablet, granule or tablet.

The present invention will now be exemplified with reference to the following Examples, by way of illustration only.

FIGURES

Figure 1. is a graph showing the in-vitro release profile of the type A lansoprazole pellets of Example 1 in pH 6.5 phosphate buffer.

Figure 2. is a graph showing the in-vitro release profile of the type B lansoprazole pellets of Example 1 in pH 6.5 phosphate buffer.

Figure 3. is a graph showing the in-vitro release profile of lansoprazole formulations A and B of Example 2 in pH 6.5 phosphate buffer.

Figure 4. is a graph showing the in-vivo release profile of lansoprazole formulations A and B of Example 2.

Figure 5. is a graph showing the in-vitro release profile of a single lansoprazole minitablet of Example 3 in pH 6.5 phosphate buffer.

Example 1: Preparation of pellets containing lansoprazole

Sugar spheres were loaded onto a Glatt granulator and were sprayed with a binder solution of hydroxypropylcellulose in isopropylalcohol. At the same time a powder blend of hydroxypropylcellulose (low sub), magnesium carbonate, lansoprazole, sucrose and corn starch was added to provide drug containing cores having the following composition:

	w/w
Sugar spheres	30.6 %
HPC	1.8 %
Lansoprazole	17.7 %
Magnesium carbonate	13.2 %
Hydroxypropyl cellulose (low sub)	8.3 %
Sucrose	17.7 %
Corn Starch	10.6 %

The resulting drug containing cores were sieved and returned to the rotor. A suspension of hydroxypropylcellulose in isopropylalcohol and croscarmellose sodium and was sprayed onto the cores to provide disintegrant layered cores having the following composition:

	w/w
Croscarmellose sodium	22.9 %
Hydroxypropyl cellulose	5.7 %
Drug containing core	71.4 %

The disintegrant coated cores were sieved and placed in a fluidisation chamber operating in a Würster mode. A polymer coat consisting of Eudragit RS and suspended talc was sprayed onto the cores continuously to provide pellets having the following compositions:

Type A	w/w
Eudragit RS	14.0 %
Talc	28.1 %
Disintegrant layered core	57.9 %

Type B	w/w
Eudragit RS	17.1 %
Talc	34.1 %
Disintegrant layered core	48.8 %

The in-vitro dissolution profile of the two types of pellets was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results are presented in Table 1.

Table 1: Dissolution profiles for delayed release pellets

	% Release:	
Time (min)	Type A Pellet	Type B Pellet
0	0	0
60	0	0
120	0.2	0
180	0.3	0
240	1.0	0
300	4.9	0
360	18.6	0.2
390	29.6	2.6
420	39.4	6
450	49.1	11.5
480	56.5	18.7
510	62.4	28
540	67.1	38.3
570	70.4	47
600	73.7	54.5
630	76.6	61.1
660	79.4	66.7
690	81.8	71.1
720	83.9	74.3
750	85.7	76.7
780	87.5	78.8
810	89.1	80.6
840	90.5	82.3
870	91.8	83.9
900	93.0	85.8
930	94.2	87.3
960	95.4	88.6

These results are presented in Figures 1 and 2.

Example 2: Preparation of a mixture of: pellets according to Example 1 and immediate release pellets

The method described above was repeated to provide drug containing cores having the following composition:

	w/w
Sugar spheres	36.7 %
HPC	0.5 %
Lansoprazole	10.0 %
Magnesium carbonate	7.5 %
Hydroxypropyl cellulose (low sub)	13.3 %
Sucrose	19.9 %
Corn Starch	12.1 %

An enteric coat was added to the drug containing core in the following proportions:

	w/w
Drug containing core	81.2 %
Eudragit L30D-55	12.1 %
Talc	3.8 %
Polyethylene glycol 6000	1.2 %
Titanium dioxide	1.2 %
Polysorbate 80	0.5 %

The in-vitro dissolution profile of the resulting immediate release pellets was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The immediate release pellets were then mixed with the pellets prepared according to Example 1 and incorporated into capsules to provide two formulations:

Formulation A:	Type A pellets and Immediate release pellets
Formulation B:	Type B pellets and Immediate release pellets

The in-vitro dissolution profile of the two formulations was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results are presented in Table 2.

Table 2: Dissolution profiles for formulations comprising immediate release pellets and delayed release pellets

Time (Mins)	Mean Drug Release (%)	
	Formulation A	Formulation B
60	27	33
120	39	44
180	44	46
240	47	48
300	53	49
360	64	51
420	74	54
480	81	62
540	85	71
600	89	80
660	92	87
720	95	93
780	98	98

These results are presented in Figure 3.

In-vivo mean concentrations of lansoprazole concentrations were measured in healthy male adults aged 18 to 45 and within 10% of desirable weight. A five way open, randomised, placebo controlled, cross over study was performed and the results obtained from the subjects treated with capsules comprising approximately two hundred pellets, equivalent to a total dose of 30 mg. The results are presented in Figure 4. In addition to the results for formulations A and B the graph includes data for Zoton ™ (a lansoprazole formulation having a conventional enteric coat) and formulation C (formulation A pellets coated with an enteric coat). These additional formulations were tested for comparative purposes.

Example 3: Preparation of delayed release minitablets containing lansoprazole

A dry granulation was prepared from lansoprazole, lactose, microcrystalline cellulose and magnesium stearate by mixing and dry granulation. A second granulation containing magnesium carbonate, crospovidone and hydroxyporpylcellulose was prepared by wet granulation . The wet granulation product was dried and milled to an appropriate size before mixing with the product of the dry granulation. The resultant blend was compressed into minitablets of 4 mm diameter using standard tooling on a Kilian LX tablet press.

	mg	w/w
Magnesium carbonate	2.24	7.47 %
Croscarmellose sodium (AcDisol)	1.2	4.00 %
Hydroxypropyl cellulose	0.9	3.00 %
Lansoprazole	3.0	10.0 %
Lactose Fast Flo	11.225	37.42 %
Microcrystalline Cellulose (Avicel PH101)	11.225	37.42 %
Magnesium stearate	0.21	0.70 %

The uncoated minitablets were coated, as described in Example 1, with Eudragit and talc:

	w/w
Eudragit RS	7.5%
Talc	15.2 %
Uncoated minitablets	77.3%

The in-vitro dissolution profile of a single minitablet was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results are presented in Table 3.

Table 3: Dissolution profile for a single minitablet

Time (Mins)	Mean Drug Release (%)
240	0
270	0
300	0
330	0
360	0
390	0
420	4.7
450	29.9
480	30.6
510	48.7
540	54.4
570	58.1
600	60.7
630	63.1
660	65.5
690	67.2
720	69.9
750	72.2
780	73.7
840	79.0
900	81.7
960	85.1

These results are presented in Figure 5.

CLAIMS

1. A solid dose unit for the delayed release of a drug characterised in that it comprises:

a) a core comprising the drug and at least one disintegrant

and b) an outer semi-permeable membrane surrounding the core which comprises a permeable water insoluble polymer and at least 50 % by weight glidant.

2. A solid dose unit as claimed in Claim 1 characterised in that when the unit is subjected to in-vitro exposure to simulated intestinal fluid minimal drug is released until after at least four hours exposure and substantially all of the drug is released after 24 hours exposure.

3. A solid dose unit as claimed in Claim 2 characterised in that minimal drug is released until after at least six hours exposure.

4. A solid dose unit as claimed in Claim 2 or Claim 3 wherein the glidant is talc.

5. A solid dose unit as claimed in any one of Claims 1 to 4 which lacks an enteric coat.

6. A solid dose unit as claimed in any one of Claims 1 to 5 which comprises a proton pump inhibitor.

7. A solid dose unit as claimed in any one of Claims 1 to 6 which is a pellet, granule, minitablet or tablet.

8. A plurality of solid dose units as claimed in any one of Claims 1 to 7 which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after four hours exposure less than 10% of the drug is released

ii) after ten hours exposure at least 30% drug is released

and iii) after 24 hours exposure at least 70% drug is released.

9. A plurality of solid dose units as claimed in Claim 8 wherein after six hours exposure less than 10% of the drug is released.

10. A plurality of solid dose units as claimed in Claim 8 or Claim 9 wherein after 20 hours exposure at least 70% of the drug is released.

11. A plurality of solid dose units as claimed in Claim 8 wherein after 8 hours exposure less than 10% of the drug is released, after 12 hours exposure at least 30% is released and after 20 hours exposure at least 70% is released.

12. A plurality of solid dose units as claimed in any one of Claims 1 to 7 which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid: after 10 hours exposure less than 10% of the drug is released, after 14 hours exposure at least 30% is released and after 22 hours exposure at least 70% is released.

13. A plurality of solid dose units as claimed in any one of Claims 1 to 7 which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid: after 12 hours exposure less than 10% of the drug is released, after 16 hours exposure at least 30% is released and after 24 hours exposure at least 70% is released.

14. A plurality of solid dose units as claimed in Claim 8 wherein after four hours exposure less than 5% of the drug is released, after ten hours exposure at least 35% is released and after 20 hours exposure at least 75% is released

15. A plurality of solid dose units as claimed in Claim 8 wherein after six hours exposure less than 5% of the drug is released, after ten hours exposure at least 35% is released and after 20 hours exposure at least 75% is released.

16. An oral formulation for the controlled release of a drug which comprises solid dose units as claimed in any one of Claims 1 to 15.

17. An oral formulation for the controlled release of a drug which comprises a first population of solid dose units comprising the drug and a second population of solid dose units comprising the drug wherein the first population

comprises units which exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after two hours exposure at least 60% of the total drug included in the first population is released

and ii) after three hours exposure at least 80% of the total drug included in the first population is released

and the second population comprises units as claimed in any one of Claims 1 to 15.

18. An oral formulation as claimed in Claim 16 or Claim 17 which is a tablet or capsule.

19. An oral formulation as claimed in any one of Claims 16 to 18 suitable for once daily administration.

20. An oral formulation as claimed in any one of Claims 16 to 19 suitable for controlling gastric pH over a 24 hour period.

21. An oral formulation as claimed in any one of Claims 16 to 20 capable of controlling gastric pH over a 24 hour period so as to prevent the pH falling below 4.0 over this period.

22. A composition comprising a permeable water insoluble polymer and at least 50 % by weight glidant suitable in the preparation of a solid dose unit as claimed in any one of Claims 1 to 15.

23. A process for the preparation of solid dose units as claimed in any one of Claims 1 to 16 which comprises coating a core comprising a drug and a disintegrant with a composition comprising a permeable water insoluble polymer and at least 50 % by weight glidant.

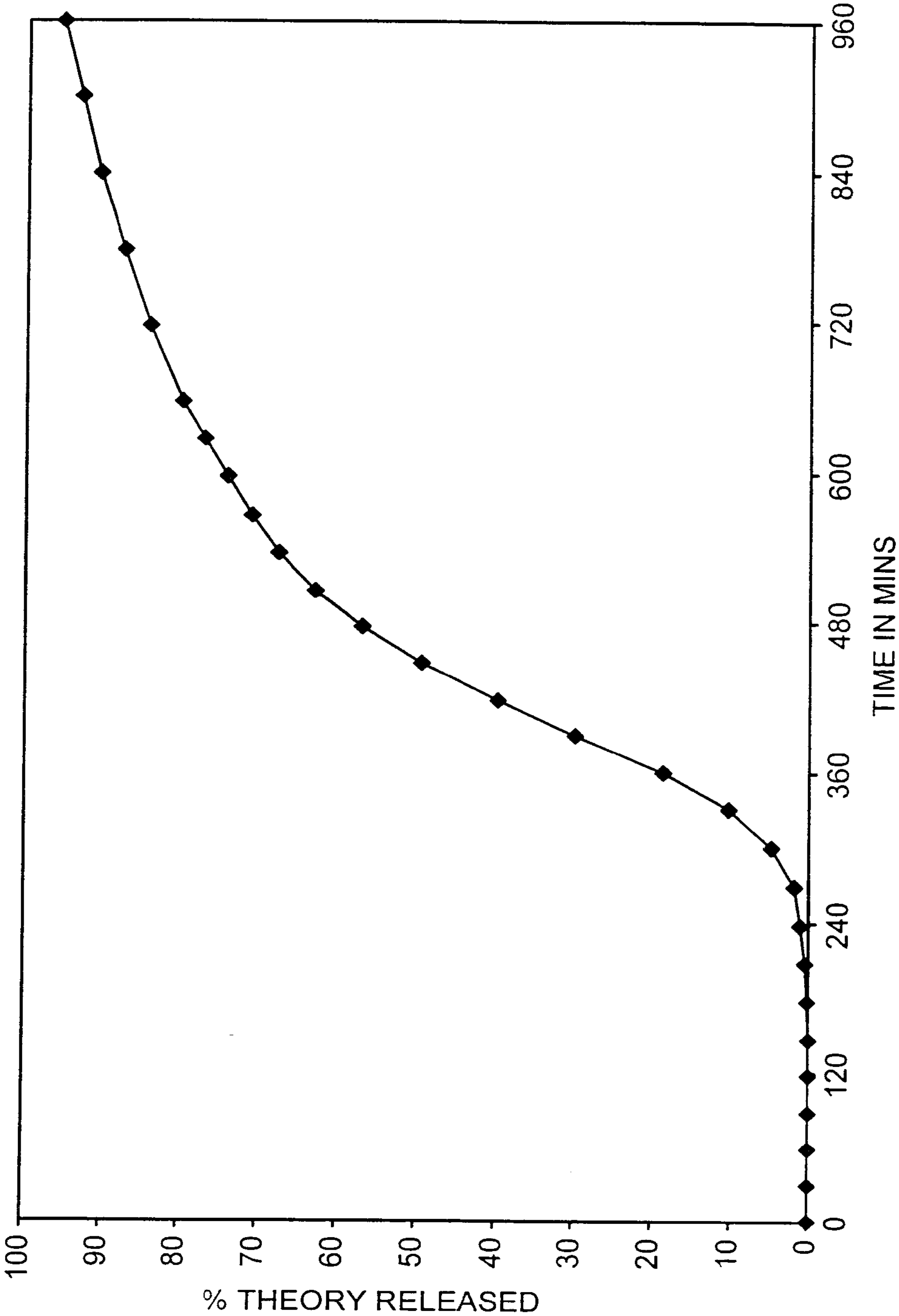
% THEORY RELEASED
0
10
20
30
40
50
60
70
80
90
100
TIME IN MINS
0
120
240
360
480
600
720
840
960

FIG. 1

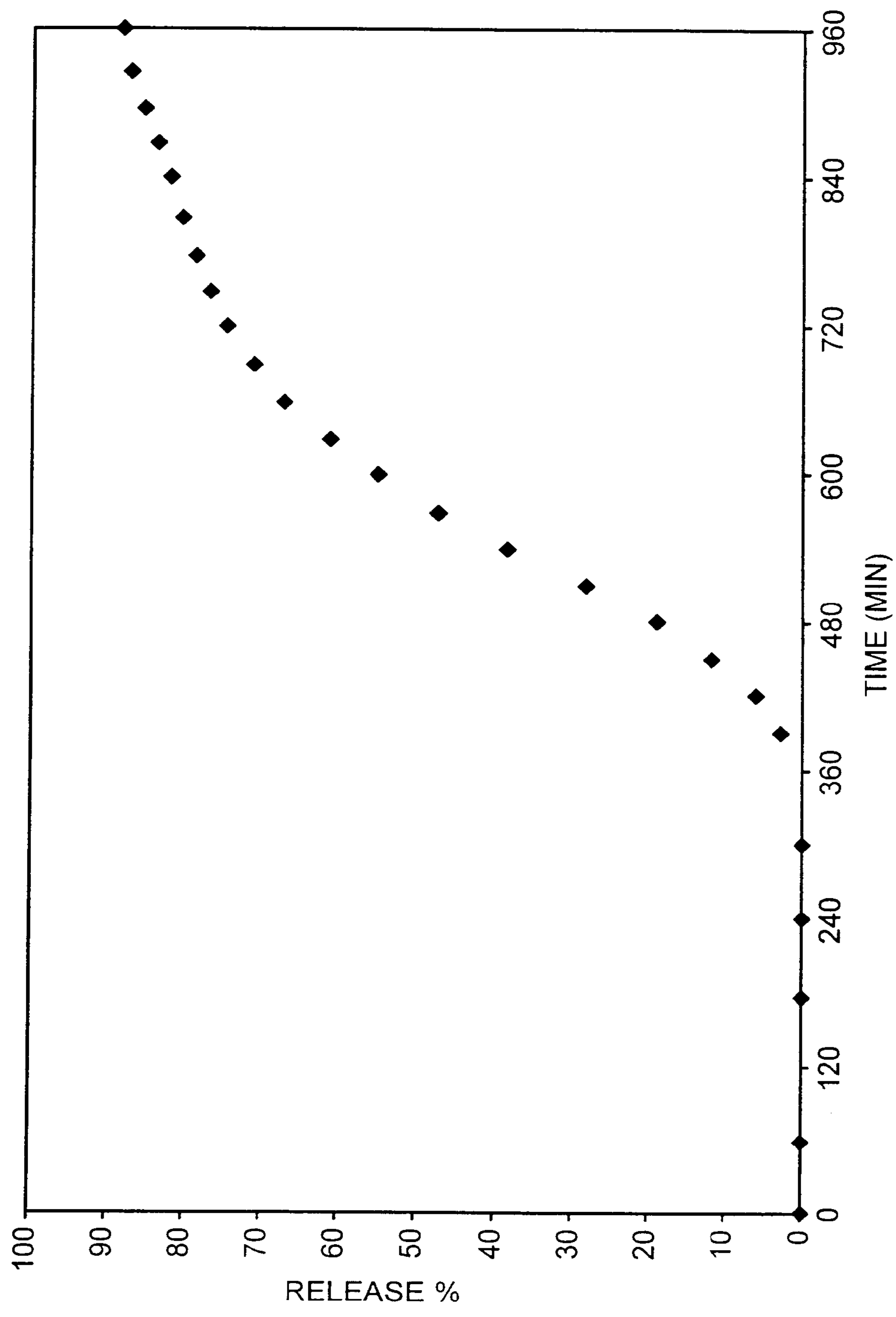
100
90
80
70
60
50
40
30
20
10
0
RELEASE %
0
120
240
360
480
600
720
840
960
TIME (MIN)

FIG. 2

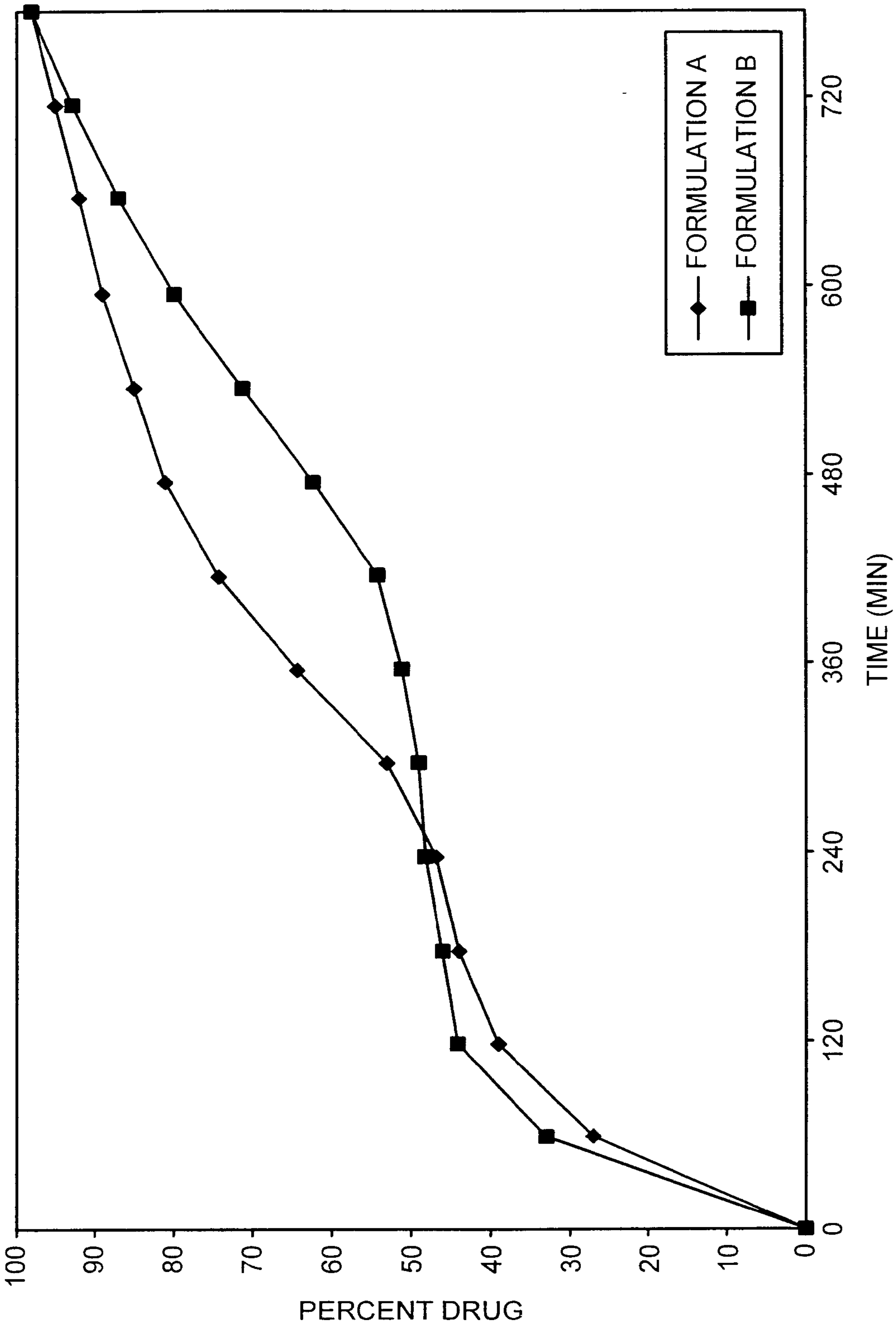
FORMULATION A
FORMULATION B
PERCENT DRUG
0
10
20
30
40
50
60
70
80
90
100
TIME (MIN)
0
120
240
360
480
600
720

FIG. 3

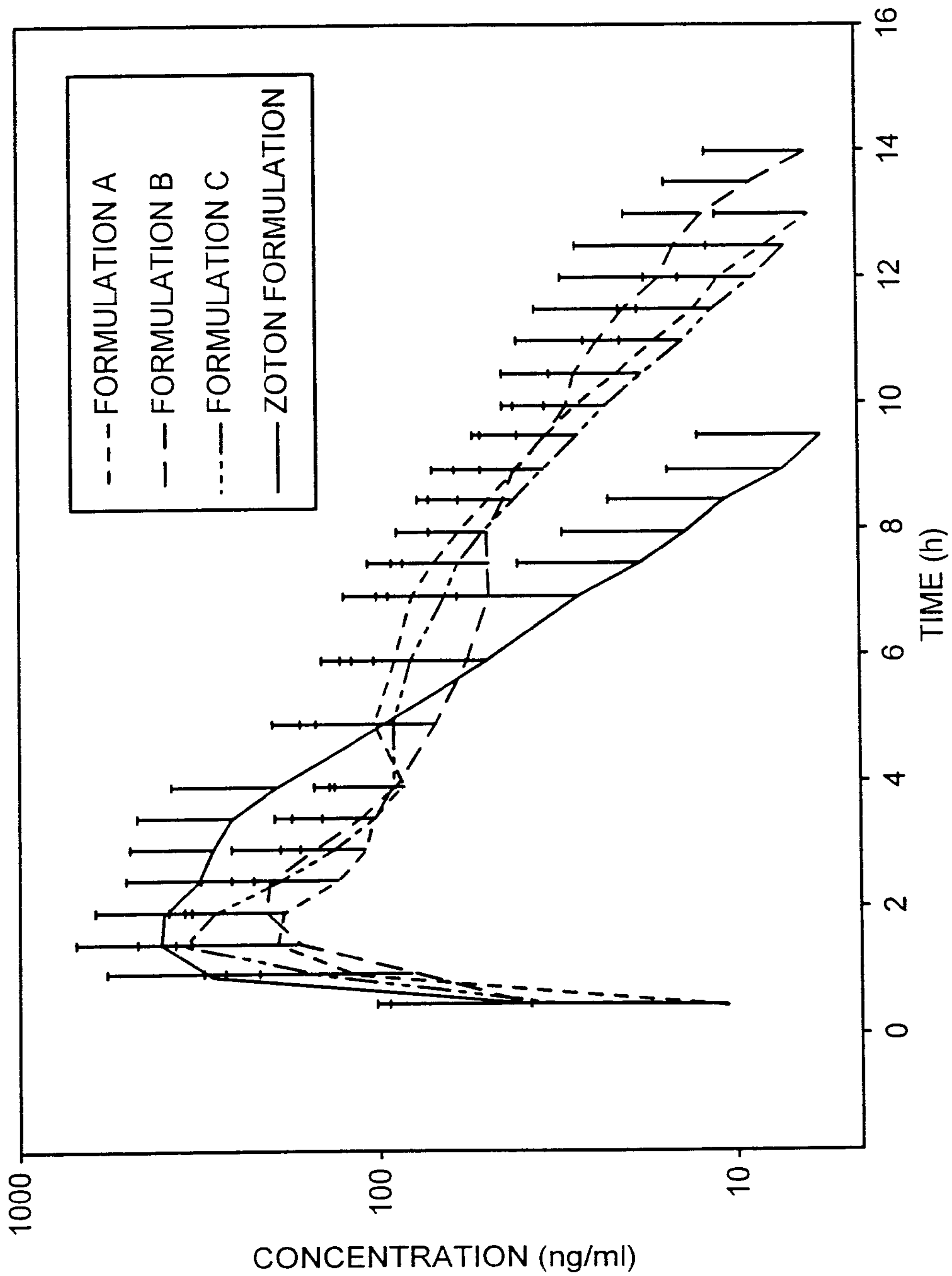
FORMULATION A
FORMULATION B
FORMULATION C
ZOTON FORMULATION
CONCENTRATION (ng/ml)
1000
100
10
TIME (h)
0
2
4
6
8
10
12
14
16

FIG. 4

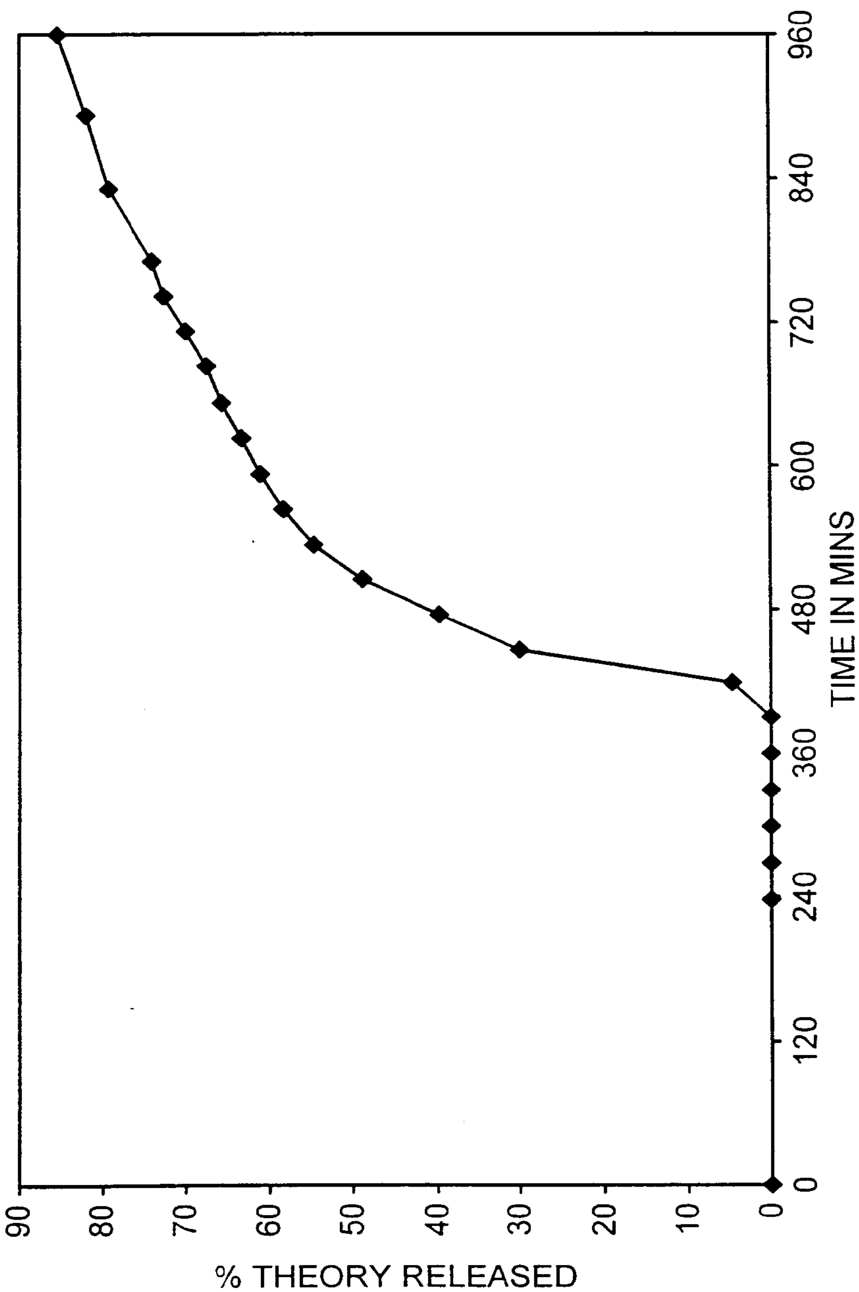
% THEORY RELEASED
90
80
70
60
50
40
30
20
10
0
TIME IN MINS
0
120
240
360
480
600
720
840
960

FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/09576

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/28 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 32093 A (ASTRA) 1 July 1999 (1999-07-01) claims 1,4,7,12,16 figures 1-5 example 1 page 15, line 4 - line 15 ---	1-23
A	WO 94 02140 A (YOSHITOMI) 3 February 1994 (1994-02-03) the whole document ---	1-23
A	WO 93 25204 A (ETHYPHARM) 23 December 1993 (1993-12-23) the whole document -----	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2001	26/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/09576

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9932093 A	01-07-1999	AU 1991399 A	12-07-1999
		BR 9814389 A	10-10-2000
		CN 1284868 T	21-02-2001
		EP 1043977 A	18-10-2000
		HR 20000381 A	31-12-2000
		NO 20003219 A	22-08-2000
		ZA 9811234 A	22-06-1999
WO 9402140 A	03-02-1994	AU 4513393 A	14-02-1994
		JP 7033659 A	03-02-1995
WO 9325204 A	23-12-1993	FR 2692146 A	17-12-1993
		AT 149835 T	15-03-1997
		AU 669719 B	20-06-1996
		AU 4332193 A	04-01-1994
		CA 2138149 A	23-12-1993
		CN 1086130 A,B	04-05-1994
		CZ 9403165 A	17-05-1995
		DE 69308849 D	17-04-1997
		DE 69308849 T	04-09-1997
		DK 646006 T	13-10-1997
		EP 0646006 A	05-04-1995
		ES 2052458 A	01-07-1994
		FI 945904 A	15-12-1994
		GR 1001535 B	31-03-1994
		GR 3023391 T	29-08-1997
		JP 7508509 T	21-09-1995
		MD 960332 A	31-03-1998
		MX 9303612 A	29-04-1994
		NZ 253179 A	28-05-1996
		PL 172706 B	28-11-1997
		RU 2103995 C	10-02-1998
		SK 155194 A	08-01-1997
		US 5385739 A	31-01-1995
		ZA 9304266 A	09-02-1996